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Chapter

TLR Signaling on Protozoan and Helminthic Parasite Infection

Chandrani Fouzder, Alpana Mukhuty, Snehasis Das and Dipanjan Chattopadhyay

Abstract

Toll-like receptors (TLRs), a major component of innate immune system, are expressed as membrane or cytosolic receptors on neutrophils, monocytes, macrophages, dendritic cells (DCs), B lymphocytes, Th1, Th2, and regulatory T lymphocytes. It recognizes pathogen-associated molecular patterns (PAMPs) and Toll-interleukin1 (IL-1) receptor (TIR) of various invading pathogens. Downstream signaling of TLRs activates NF-κB, which acts as a transcription factor of pro-inflammatory cytokines, chemokines, and costimulatory molecules. A balance between pro- and anti-inflammatory cytokine protects host body from infectious agents and also induces the healing process. Some of parasitic infections by protozoans and helminths such as Malaria, Leishmaniasis, Trypanosomiasis, Toxoplasmosis, Amoebiasis, Filariasis, Schistosomiasis, Ascariasis, Taeniasis, and Fasciolosis are the leading cause of death and economic loss in both developing and developed nations. Frequent exposure to parasites, immigration, refugee resettlement, increasing immunodeficiency, climate change, drug resistance, lack of vaccination, etc. are the major cause of emerging and re-emerging of the above-stated diseases. However, TLR activation by parasites could stimulate antigen presenting cells and ultimately clear the pathogens by phagocytosis. So, a better understanding of host-parasite interaction in relation to TLR signaling pathway will improve the controlling method of these pathogens in immunotherapy.

Keywords: Toll-like receptors, pathogen-associated molecular patterns, protozoan parasite, helminth infection

1. Introduction

Increasing cases of parasitic infections (due to protozoans and helminths) and high rate of mortality are the greatest problem of today's world. Some of these diseases such as Malaria, Filariasis, Trypanosomiasis, Leishmaniasis, Toxoplasmosis, Amoebiasis, Ascariasis, Schistosomiasis, and Taeniasis affect over half a billion people worldwide and cause economic loss in both developing and developed countries [1]. Overpopulations, migration of people into large urban areas, and unhygienic environment are the main reasons for making these diseases epidemic [2]. However, the tragedy is that only 5% of total health expenditure was given for research work on parasitic diseases [3]. Currently, there is no effective vaccine available for these major problems. So, a better understanding of pathogenesis during infection, resistance mechanism of pathogens, host protective immune response initiation, and progression is needed for developing effective vaccines or therapeutic interventions [4].

Among the two types of vertebrate immune system, innate immunity provides the first line of defense against parasites. Previous studies stated innate immunity as nonspecific response, and it induces the acquired immunity (slower and specific response) by providing pathogens to T and B cells [5]. However, recent evidence proved that innate immune system also had a great degree of specificity and can provide host defense against invading parasites. This is because of the presence of five classes of pattern recognition receptors: TLRs (Toll-like receptors), C-type lectin receptors, NOD-like receptors (nucleotide-binding oligomerization domain leucine-rich repeat-containing receptors), RIG-I (retinoic acid inducible gene I protein) helicase receptors, and cytosolic dsDNA sensors [6, 7]. Among them, TLRs form a bridge between innate and adaptive immunity and play a very important role in parasite eradication. TLRs recognize specific pathogen-associated molecular patterns (PAMPs) in pathogens and initiate opsonization, phagocytosis, pro-inflammatory and anti-inflammatory response, and apoptosis [7, 8].

2. Cells expressing TLRs

TLRs, a major component of innate immunity, are Type-1 transmembrane glycoproteins present in both vertebrates and invertebrates [9]. Toll-like receptors are named due to their similarity with Drosophila Toll protein (Toll) [10]. All TLRs have a highly variable extracellular domain containing leucine-rich repeat (LRR) domain for ligand binding and intracellular TIR homology domain [11]. Toll-like receptors and interleukin-1 receptor together form "Interleukin-1 receptor/Toll-like receptor" superfamily whose all members have a common Toll-IL-1 receptor (TIR) domain [12]. Till date, 10 humans and 12 mice functional TLRs were identified. Although humans and mice have similar TLR1–9, TLR10 is nonfunctional in mice and TLR11–13 are lost in humans [13]. TLR1, TLR2, TLR4, TLR5, and TLR6 recognize extracellular PAMPs, which are expressed on cell surface, whereas TLR3, TLR7, TLR8, and TLR9 are expressed within endoplasmic reticulum (ER), endosomes, lysosomes, and endolysosomes and identify nucleic acids [14]. The presence of TLRs on specific intracellular vesicles restricts their activation by self-nucleic acids released by apoptotic cells [15]. TLR11 (a relative of TLR5) and TLR13 are expressed in intracellular vesicles [16], but cognate PAMP of TLR13 has not been identified yet [17]. **Table 1** shows the distribution of various TLRs in different cells.

TLRs can be classified on the basis of their recognized ligands—TLR1/TLR2 heterodimer (triacylated lipopeptides), TLR2/TLR6 heterodimer (diacylated lipopeptides), TLR4 (lipopolysaccharide), TLR3 (double-stranded RNA), TLR5

Cells	Expressing TLRs
Neutrophils	TLR 1, 2, 4, 5, 6, 7, 8
Monocytes/macrophages	TLR 1, 2, 4, 5, 6, 7, 8
Myeloid dendritic cells	TLR 2, 3, 4, 7, 8
Plasmacytoid dendritic cells (PDCs)	TLR 1, 6, 7, 9
B lymphocytes	TLR 1, 3, 6, 7, 9, 10
T lymphocytes (Th1/Th2)	TLR 2, 3, 5, 9
T lymphocytes (regulatory)	TLR 2, 5, 8
Peripheral blood mononuclear cell (PBMC)	TLR 2, 4, 5, 7, 8, 9

Table 1.
Different Toll-like receptors expressed by immune cells [7, 16].

(flagellin), TLR 7/8 (single-stranded RNA), and TLR9 (unmethylated CpG motif) [18, 19]. These ligands for TLRs are of bacterial, viral, protozoan, fungal, and helminth membrane bound or endogenously released molecules such as hyaluronic acid, fibrinogen, fibronectin, b-defensins, heparan sulfate proteoglycans, heat shock proteins, nucleic acids, and synthetically derived molecules [20].

3. TLR signaling pathway

TLRs present on dendritic cells (DCs) [both myeloid DCs (mDCs) and plasmacytoid DCs (pDCs)], neutrophils, macrophages, natural killer (NK), and natural killer T (NKT) cells induce dendritic cell maturation, MHC molecule upregulation, and costimulatory molecule production (CD40, CD80, and CD86) [21, 22]. The cytokines released by TLR signaling ultimately activate Th1 cells (via IL-12 from DCs) and Th2 cells (via IL-4 from B cell) [21, 23].

Toll-interleukin-1 receptor (TIR) domain is responsible for transducing the signal from TLRs to their adaptor proteins. The C-terminus of all TLRs, IL-1 and IL-18 and adaptor proteins of TLRs have this TIR domain. Six adaptor proteins involved in TLR signaling are MyD88 (myeloid differentiation factor 88), TIRAP (Toll-IL-1 receptor domain-containing adaptor protein) and MAL (MyD88 adapter-like), TRIF (TIR domain-containing adaptor inducing interferon-β) and TICAM-1, TRAM (TRIF-related adaptor protein) and TICAM-2, SARM (sterile-α and HEAT/Armadillo motifs-containing protein) and MyD88-5, and BCAP (B Cell Adaptor for PI3K) [24]. TLR signaling occurs via two separate pathways: MyD88 (myeloid differentiation primary response protein)-dependent pathway and MyD88-independent pathway. MyD88-dependent pathway stimulates all TLRs except TLR-3, which gets stimulated by MyD88-independent pathway. However, in case of TLR4, both MyD88-dependent and independent pathways operate [25]. MyD88 (an adaptor molecule) activates IRAK-4 (interleukin-1 receptor-associated kinase-4) alone or in combination with TIRAP (Toll-IL-1 receptor domain-containing adaptor protein) or MAL (MyD88

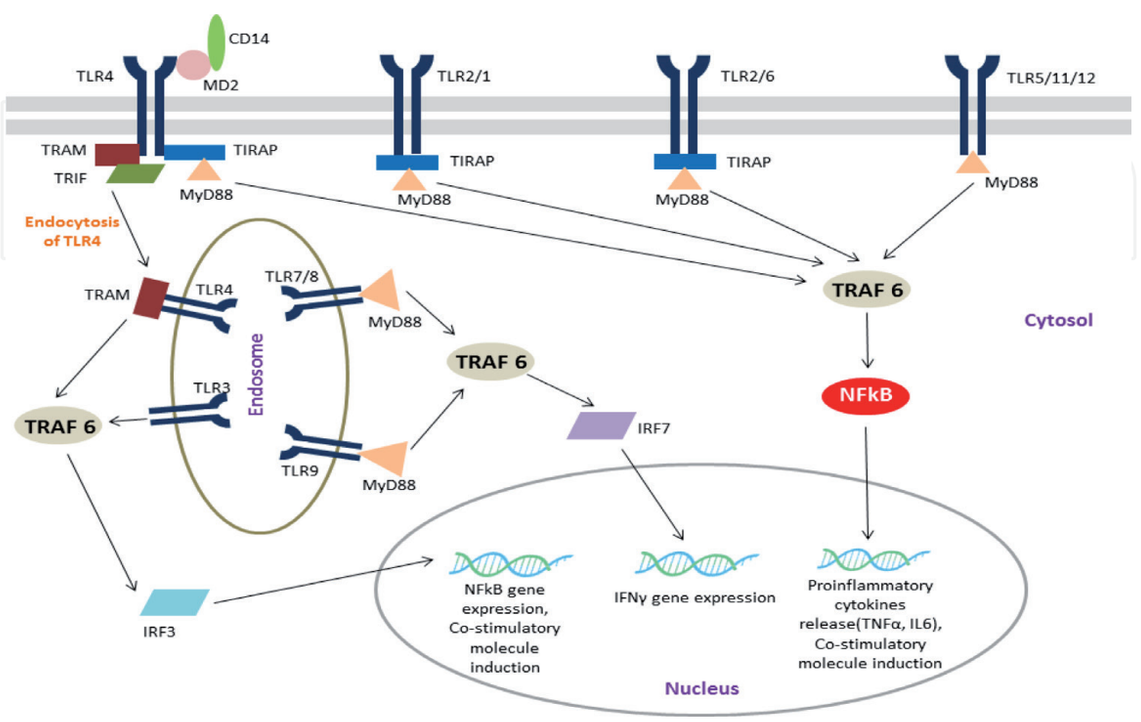

Figure 1.
TLR signaling pathway.

adapter-like). Then, IRAK-4 phosphorylates IRAK-1 [26] which in turn phosphorylates IRAK-2. IRAK-2 ubiquitinates TRAF6 (tumor necrosis factor receptor-associated factor 6) and induces two signaling pathways: (1) AP-1 (activator protein 1) activation via MAK 4/7 (mitogen-activated protein kinase) phosphorylation and (2) TAK1 (transforming growth factor-β-activated kinase 1) activation ultimately leads to MAPK (mitogen-activated protein kinase) and IKK complex [27] stimulation and nuclear factor κB (NF-κB) translocation inside the nucleus via degradation of its inhibitor. Both AP-1 and NF-κB induce the expression of pro-inflammatory cytokines and chemokines. A different MyD88-dependent pathway stimulates TLR 7, 8, and 9, which acts as a ligand for viral nucleic acids. MyD88-associated IRAK1 (interleukin-1 receptor-associated kinase-1) phosphorylates IRF7 (interferon-regulatory factor-7), which regulates Type I interferon expression [28]. TLR signaling through MyD88-independent pathway occurs via two adaptor molecules—TRIF (Toll-IL-1 receptor domain-containing adaptor inducing interferon-β) and TRAM (TRIF-related adaptor molecules) (**Figure 1**). This induces Type 1 interferon by IRF-3 (interferon-regulatory factor-3), NF-κB activation, and expression of co-stimulatory molecules [29].

4. Protozoan infections

Different protozoan (Plasmodium, Leishmania, Trypanosoma, Toxoplasma, and Entamoeba) PAMPs induced pathogenic reactions through TLR signaling pathway.

4.1 Malaria

Malaria, one of the most life-threatening diseases of human history, has infected about 219 million people over 90 countries with around 1 million deaths per year. Plasmodium, an intracellular protozoan parasite, is the causative agent of malaria. It is transmitted by infected female Anopheles mosquito biting, and four species of *Plasmodium* are responsible for human malarial infection. Among *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale,* and *Plasmodium malariae*, *P. falciparum* is the deadliest. Recently, another species named *Plasmodium knowlesi* has been found to infect humans [30]. In the early presymptomatic stage, a very low level of plasmodium can induce inflammatory response [31]. The innate immune genes such as TLRs, PRRs, and inflammatory cytokines are already upregulated, and these lead to elevate the level of TNF, IFN, and IL-12 from plasmodium-infected peripheral blood mononuclear cells (PBMCs) up to 48 h of infection [32, 33]. These inflammatory responses are associated with the pathophysiological condition and clinical symptoms of malaria including anemia, cerebral malaria, and ultimate death [34]. Cerebral malaria is caused due to overexpression and binding of adhesion molecules such as intracellular adhesion molecule 1 (ICAM-1), vascular cellular adhesion molecule 1 (VCAM-1), endothelial/leukocyte adhesion molecule (ELAM-1), and CD36 [35] on brain endothelial cell receptors. Thus, inflammatory response leads to sequestration of infected red blood cells in host brain [36]. Furthermore, TNF and IFN suppress hematopoiesis and lead to anemia during malarial infection [37]. The potential immunomodulators of the malarial parasites are: (1) plasmodial glycosylphosphatidylinositol (GPI) anchors, (2) hemozoin, and (3) plasmodial DNA. All of these three molecules are referred as "malaria toxin" released during schizogony and cause inflammation and symptoms of malaria [38, 39].

Homodimer of TLR4 and heterodimer of TLR1/TLR2 and TLR4/TLR6 can bind to GPIs released during erythrocytic phase of *P. falciparum* infection [40]. GPI induces TLR-mediated proinflammatory cytokines (TNFα and IL-1) [41] and

nitric oxide [42] release from macrophages. It also induces cerebral malaria at later course of infection [43]. Plasmodium 2-Cys peroxiredoxin also acts as a TLR4 ligand in monocyte and mast cells and causes cytokine production [44]. Hemozoin is released during each life cycle of *P. falciparum* infection and makes a complex with plasmodial DNA. This complex acts as a TLR9 ligand and leads to the production of proinflammatory cytokines (TNFα and IL-1β) [45]. Hemozoin DNA complex induces cerebral malaria by caspase 1-mediated inflammasome (NLRP3) formation by TLR9 in case of *P. chabaudi* infection [46] but is absent in *P. berghei* spoprozoite infection [47]. Although in case of both mice and humans, Plasmodium infection renders no TLR stimulation in dendritic cells. The infant exposed to TLR-mediated cytokine profiles (IL-10) is associated with higher risk of *P. falciparum* maternal infection during delivery [48]. RNA of *P. chabaudi* acts as a ligand for TLR7 and induces IFNγ, IL-10, IL-12, and TNF release at 24 h of infection [49]. In case of *P. vivax* infection, TLR5 and TLR7 hinder parasitic growth, but TLR9 is associated with high inflammation and cytokine production [50]. The 19 kDa C-terminal fragment of merozoite surface protein 1 (MSp1) in *P. vivax* acts as a ligand for TLR5 [51]. *P. yoelii* infection in peritoneal macrophages enhances TLR and parasite-specific immune response [52] (**Figure 2**). Other than Th1 response, malaria parasite-derived molecules also induce Th2 response via IL-4-inducing factor (released by PI3K-Akt-NF-κB signaling) in DC [53].

4.2 Leishmaniasis

Leishmaniasis is one of the deadliest parasitic infections with an estimation of 200,000–400,000 worldwide infections each year. A protozoan parasite is the causative agent of this disease, which is transmitted to humans by the biting of female Phlebotomus sandfly. The pathology of this infection and causative parasitic species includes cutaneous (i.e., *L. major*, *L. mexicana*, and *L. guyanensis*), mucocutaneous (i.e., *L. amazonensis* and *L. braziliensis*), or visceral leishmaniasis (*L. donovani* and *L. chagasi*) [54]. Several reports indicate that few Leishmania-derived molecules could interact with innate immune receptors (TLRs) of host and result in inflammatory

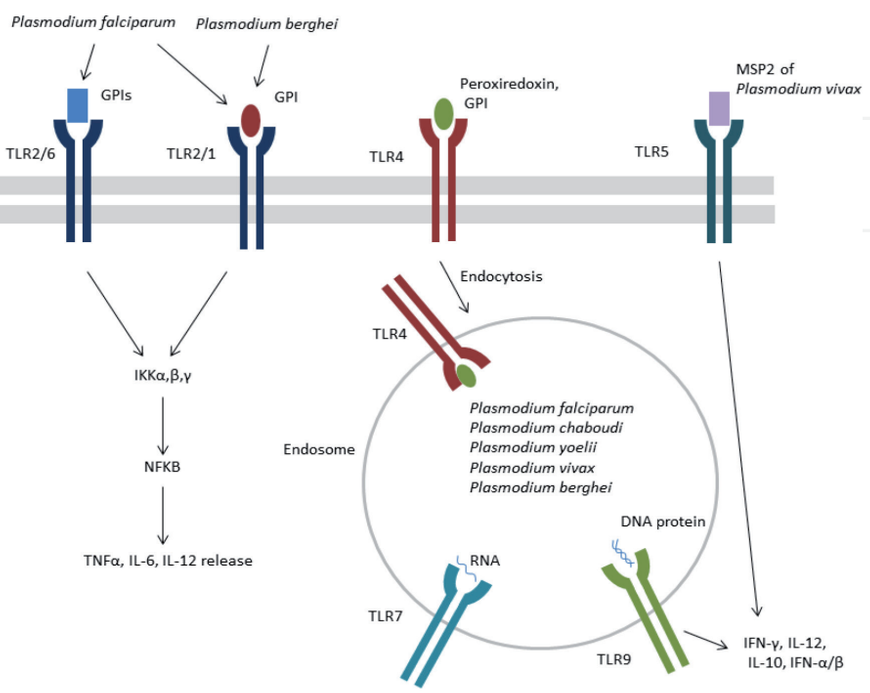

Figure 2.
TLR signaling during Plasmodium infection.

response. This inflammation effectively deprives parasites from the host by inducing efficient adaptive responses.

Lipophosphoglycan (LPG) occurs as a surface protein of *L. major*, *L. mexicana*, *L. aethiopica*, and *L. tropica* and acts as a major ligand for TLR-mediated host immune response. LPG's secreted form is structurally similar to membrane bound form with differences in sugar types of glycan and in number of phosphorylated oligosaccharide repeats. Membrane bound LPG induces ROS production and Th2 cell differentiation, whereas soluble LPG causes Th1-promoting cytokine production [55]. Inside NK cells, LPG of *L. tropica* induces TNFα, IFNγ, nitric oxide (NO), and reactive oxygen species (Th1 response) release via TLR2 upregulation and stimulation [56, 57]. TLR2 can also induce immune response by altering TLR9 expression [58]. However, in case of *L. braziliensis* and *L. amazonensis*, parasite could decrease IL-12 production, increase IL-10 production by TLR2-mediated p38 MAPK inhibition in macrophages, and thus increase pathogenesis. TLR2/TLR4 dimerization induces the expression of SOCS-1 and SOCS-3 (suppressor of cytokine signaling protein) by LPG [59]. A protein structurally related to silent information regulator 2 (SIR2) family could activate B lymphocytes, major histocompatibility complex (MHC) II, CD40 and CD86 (costimulatory molecules) overexpression, DC maturation, and TNFα and IL12 secretion through TLR2 [60]. HO-1 (heme oxygenase-1) mediated inhibition of TLR2, 4, 5, and 9 (but not TLR3) association with their adaptor proteins resulted in downregulation of TNFα and IL-12 production in *L. chagasi* and *L. donovani* infection [61]. This inflammatory imbalance occurs due to MAPKp38 phosphorylation inhibition and ERK 1/2 phosphorylation activation in macrophages. In addition, *L. donovani*, *L. mexicana* (expressed p8 proteoglycolipid complex), and *L. major* suppressed TLR4 activation by releasing TGFβ that activates A20, a complex deubiquitinating enzyme, through SRC homology region-2 domain containing phosphatase-1 (SHP-1) and IRAK inactivation [62]. Proteoglycolipid complex (P8), host-derived Apolipoprotein E (ApoE), and four glycolipids of *L. pifanoi* amastigote were the ligands of TLR4 and control the parasite [55]. P8 activates TLR4 of parasitophorous vacuole, which induces IL1 and TNFα production and aids in phagocytosis of *L. pifanoi*. At early stage of infection, neutrophil-derived serine protease and elastase results in parasite death, but at later stage, bone marrow derived macrophages (M2b macrophage) phagocytose neutrophil and helps in *L. major* replication by Th2-type response [63]. *L. panamensis* infection results in TNF α production through TLR-1, TLR-2, TLR-3, and TLR-4 pathway in human primary macrophages [64], metacyclic promastigote of *L. mexicana* induce phosphorylation of MAP kinases (ERK, p38, and JNK) through TLR4 and MΦ(bone marrow-derived macrophages), iNOS, cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), NO, and arginase-1 are act as the inflammatory response mediators [65]. Leishmania parasites grow inside the phagolysosome of the host cells, which reflect that endosomally localized TLRs are also involved in pathogenesis [66]. In case of *L. donovani* infection, TLR7 activates IRF-5 and induces Th1 responses of host [67]. Cytosine-phosphate-guanosine motifs in DNA of *L. major* induce TLR9-mediated NK cell activation and IL12 production from bone marrow-derived DC [68, 69]. Recent reports show that viral RNA present in *L. guyanensis* (LRV1-Lg), *L. major* (LRV2-Lmj) [70], and *L. aethiopica* (LRV2-Lae) serves as a ligand for TLR3 [71]. TLR3 produces NO and TNFα during *L. donovani* infection and mediates leishmanicidal activity [72] (**Figure 3**).

4.3 Trypanosomiasis

The protozoan parasites of the genus *Trypanosoma* cause a group of disease in several vertebrates, called trypanosomiasis or trypanosomosis. In humans,

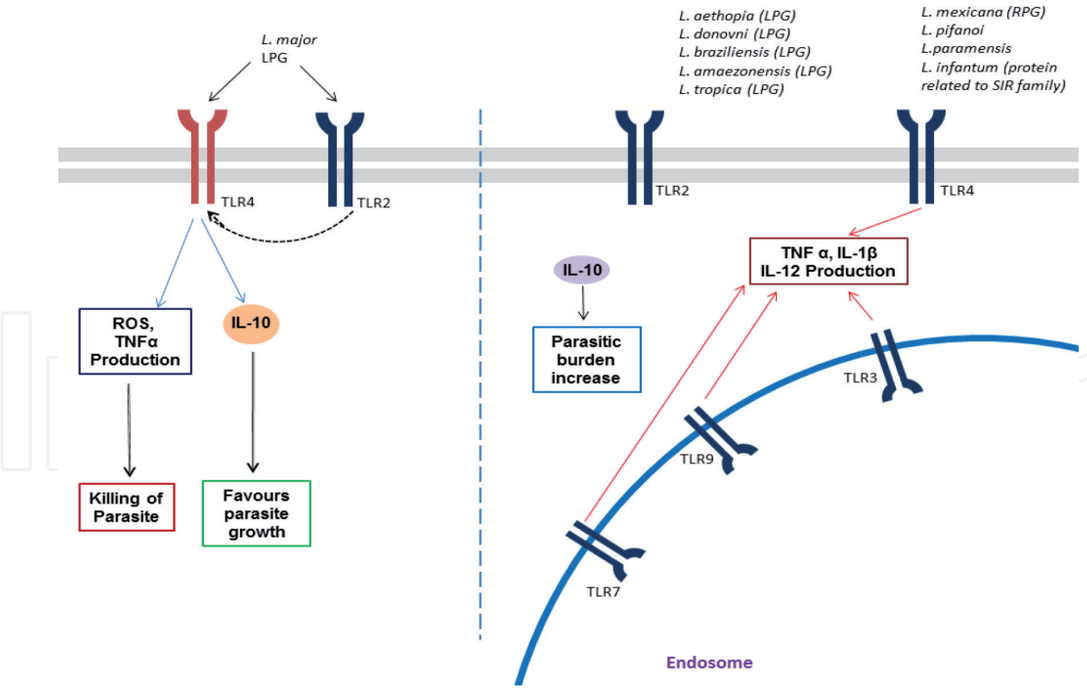

Figure 3.
TLR signaling induced by different Leishmania ligands.

Trypanosoma brucei gambiense and *Trypanosoma brucei rhodesiense* cause African trypanosomiasis or sleeping sickness (transmitted by tsetse fly), and *Trypanosoma cruzi* causes American trypanosomiasis or chagas disease (blood feeding Triatominae bugs) [73]. All of these parasites cause millions of death per year in both sub-Saharan African and Latin American countries. The disease remains asymptomatic for several years and ultimately affects the central nervous system, heart, and GI tract [74].

TLR receptor plays an important role in internalization of the parasite through phagocytosis and induces immune response for parasite eradication from cells [75]. GPI anchored mucin-like glycoproteins (tGPI-mucin contains unsaturated alkyl-acylglycerol) of the *T. cruzi* trypomastigote membrane activates MAPK (by phosphorylation) and IkB (inhibitor of NF-κB), which triggers TLR2-mediated cytokine production by macrophages [76]. A TLR2-TLR6 and CD14 complex recognize the free GPI (glycoinositophospholipids containing ceramide) from *T. cruzi* parasite (epimastigote) [77]. Tc25, a *T. cruzi* derived protein, induces TLR2-mediated pro-inflammatory cytokine release from host cells [78]. However, role of GPI anchors VSGs of *T. brucei* Trypomastigotes in specific TLR-mediated macrophage activation and proinflammatory cytokine (TNFα, IL-6, and NO) production have not been elucidated yet [79]. *T. cruzi* and *T. brucei* genomic DNA (contains unmethylated CpG motifs) have TLR9-mediated TNFα and IFNα/β stimulation and penetration of T cells in brain parenchyma [80, 81] (**Figure 4**).

4.4 Toxoplasmosis

Toxoplasma gondii, an obligate intracellular apicomplexan parasite, is a leading cause of food borne disease in a wide range of worm-blooded animals worldwide [82]. *T. gondii* causes asymptomatic toxoplasmosis in healthy adults and produces severe toxoplasmic encephalitis in immune compromised people [83]. Moreover, it causes congenital toxoplasmosis in fetus leading to death and abortion [84]. Inside its intermediate host humans, mice, etc., *T. gondii* proliferates asexually to form tachyzoite and bradyzoite stages [85].

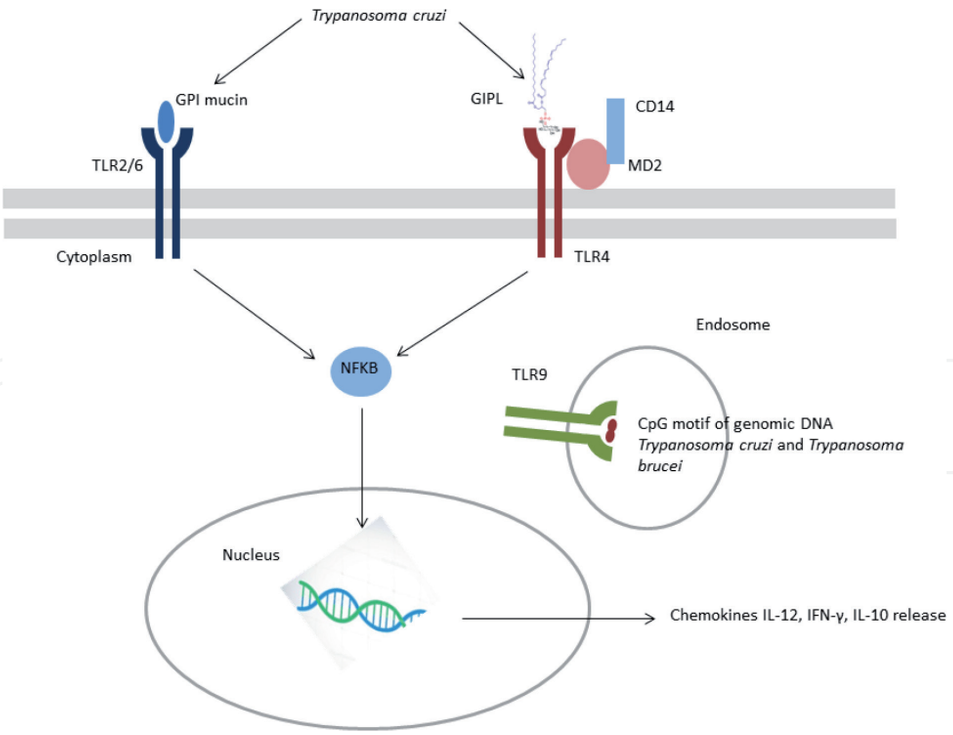

Figure 4.
Trypanosoma PAMPs and TLR signaling.

TLR11 and TLR12 recognize *T. gondii* profiling (TgPRF) and induce IL12 and IFNα production in conventional dendritic cells (cDCs), macrophages, and plasmacytoid dendritic cells (pDCs). This IFNα induces IFNγ production from NK

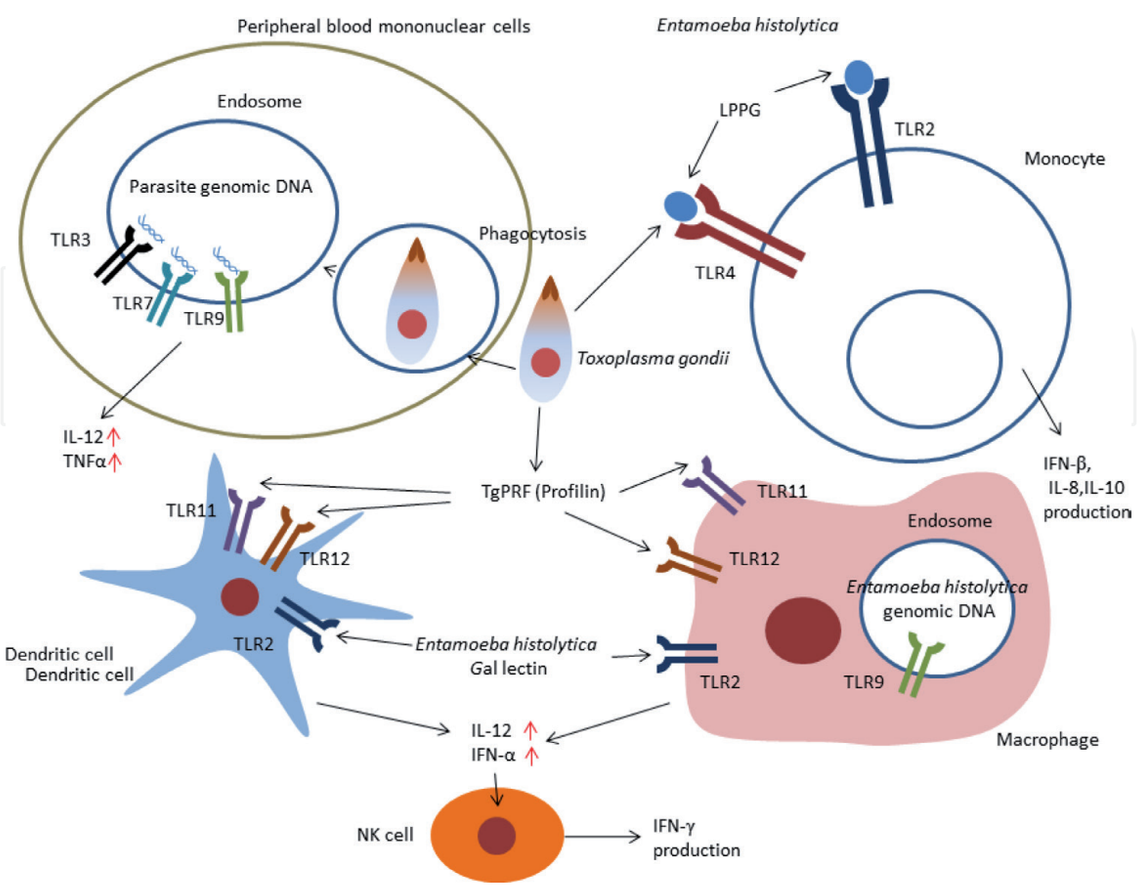

Figure 5.
Toxoplasma and Entamoeba induced TLR signaling pathway.

cells. *T. gondii* infection also induces IFNβ production in inflammatory monocytes (IMs) and TLR4-mediated phagocytic uptake of the parasite [86]. Endosomal TLRs (TLR3, TLR7, and TLR9) stimulate IL12 production in human PBMCs in response to DNA and mRNA of *T. gondii* tachyzoites when the cells were primed with IFNγ [87]. GPIs present in parasite membrane aggravate TLR2- and TLR4-mediated TNFα production in inflammatory response [88]. In some cases, tachyzoites differentiate into bradyzoites inside the central nervous system and cause neurological and behavioral abnormalities [89]. TLR2 signaling pathway makes chronic inflammation in different central nervous system cell types [85] (**Figure 5**).

4.5 Amoebiasis

Entamoeba histolytica is a protozoan parasite, which causes amebiasis in humans. It is one of the deadliest diseases after malaria and causes almost 40,000–100,000 deaths per year in underdeveloped countries [90]. The clinical symptoms include diarrhea, dysentery, pain in lower abdomen, and liver abscess, which occur due to invasion of amoeba in host lung, heart, brain, skin, genital, etc. [91]. The lipophosphopeptidoglycan (LPPG) present on the surface of *E. histolytica* induces TLR2- and TLR4-mediated NF-κB activation and cytokine (IL-8, IL-10, IL-12p40, and TNFα) release from human monocytes [92]. The Gal/GalNAc lectin (Gal-lectin), a surface molecule of *E. histolytica,* upregulates cytokines and TLR2 genes via NF-κB and MAP kinase activation in macrophages and dendritic cells [93]. TLR9 recognizes *E. histolytica* genomic DNA and helps in TNFα production in macrophages [94] (**Figure 5**).

5. Helminth infections

Although several studies were conducted on TLR signaling in response to intracellular parasites, only a few examination reflects the interaction of helminths with TLRs.

5.1 Filariasis

Lymphatic filariasis (commonly called elephantiasis), caused by three species of nematode parasites, *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*, is a major health problem in tropical countries. During initial stage, infection remains asymptomatic. Acute condition displays local inflammation of skin, lymph nodes, and lymphatic vessels, which ultimately leads to edema in chronic condition [95]. Wolbachia, an intracellular symbiotic bacterium of filarial nematode, is the major mediator of inflammatory response in case of lymphatic filariasis and onchocerciasis [2]. WSP protein in outer membrane of *Wolbachia* sp. induces TLR2- and TLR4-mediated inflammation in macrophages and DCs [96].

In case of chronic infection, filarial nematode downregulates host immune response via TLR4-mediated T cell apoptosis [97]. Live microfilariae of *B. malayi* can downregulate mRNA and protein expression of TLR1, TLR2, TLR4, and TLR9 and activate TLR2 upon antigen stimulation on B cells and monocytes [98]. In DCs, live microfilariae and microfilarial antigen (MF Ag) diminish IL-12, IFNα, and cytokine production via inhibition of NF-κB complex formation [99]. Microfilariae infective stage (L3) of *B. malayi* also shows partial inhibition of Langerhans cells (LCs) that lead to CD4+ T cell proliferation [100]. Circulating B cells (called Breg) express TLR2 and TLR4 and maintain a worm favorable condition via induction of Treg, IL-10, and filarial-specific IgG. However, Breg-mediated response causes

asymptomatic infection in initial stages but leads to secondary infection by bacteria and virus in filarial patients [92]. A phosphocholine-containing glycoprotein (ES-62) of *Acanthocheilonema viteae* (rodent filarial nematode) inhibits B and T lymphocyte activation. The secretory ES-62 inhibits TLR4-mediated IL-12 and TNFα production [101] (**Figure 6**).

5.2 Schistosomiasis

Schistosomiasis is a worldwide distributed parasitic disease caused by a flatworm, Schistosoma. It accounts for 260 million infected people in tropical and sub-tropical regions (Africa, South America, the Middle East, East Asia, and the Philippines) [102]. *S. mansoni*, *S. intercalatum*, *S. haematobium*, *S. japonicum,* and *S. mekongi* are the five species of schistosomes that cause disease in humans. *S. mansoni*, *S. japonicum,* and *S. intercalatum* are responsible for intestinal schistosomiasis, while *S. haematobium* causes urinary schistosomiasis and is most important in terms of public health [102]. Fresh water snail of the genus *Bulinus* (*S. haematobium*), *Biomphalaria* (*S. mansoni*), and *Oncomelania* (*S. japonicum*) acts as an intermediate host of Schistosoma parasites [103].

S. japonicum eggs are deposited in the liver, lung, and intestinal wall of host, which induce granulomatous inflammation and progressive fibrosis. Th cells, natural killer (NK) cells, NKT cells, myeloid-derived suppressor cells (MDSCs), and macrophages are mainly involved in fight against *S. japonicum* and its eggs [104]. Expressions of TLR1, TLR3, TLR7, TLR8, and NF-κB are greatly repressed at the initial stage of schistosomiasis. TLR3 modulates Th2 response in lung in *S. mansoni* infection and in NK cells during *S. japonica* infection [105]. *S. mansoni* is known to attenuate Th1 responses (decrease IFNγ, TNFα, IL-12, and NO) but to promote Th2 immune responses (increase IL-10 and TGFβ) [106]. Although TLR4 protects the host from Schistosoma infection, TLR2 favors the parasite growth [107]. Both SEA (soluble egg antigen) and ES products of *S. mansoni* act as a strong inducer of Th2 response [108]. It induces transcription of markers CD40 and CD86 and cytokines IFNβ, TNFα, and IL-12-p40 in mouse myeloid DCs [109]. Glycans present in *S. mansoni* induce Treg by TLR2-mediated DC differentiation and IL-10 secretion [110]. Schistosoma egg product LFNP III also stimulates IL-10 production

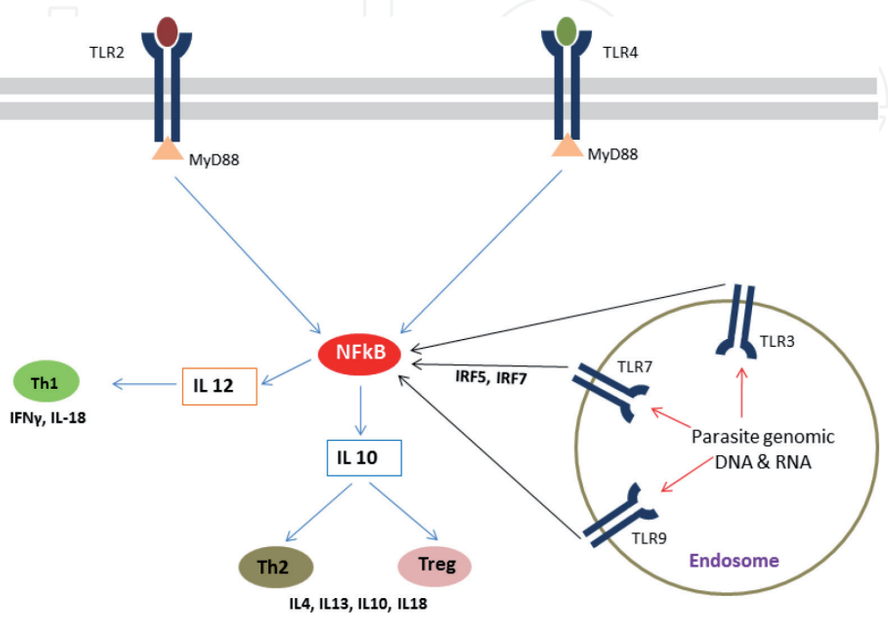

Figure 6.
TLR signaling pathway induced by Helminth pathogens.

from TLR2 and promotes Treg activation [111]. An immunomodulatory peptide, SJMHE1 of *S. japonicum*, induces TLR2-mediated Treg activation. The lysophosphatidylserine and glycolipids [112] of scistosome also activate TLR2 in DCs [113] (**Figure 6**).

5.3 Taeniasis

The pork tapeworm (*Taenia solium*) is a cestoda parasite transmitted to humans by feeding cystic larvae infected pork. Here, pig acts as an intermediate host, which swallows *T. solium* egg containing human stool and develops larva inside their body [114]. The cysticercosis cyst causes neurocysticercosis (NCC) in the nervous system, and adult taenia produces intestinal taeniasis in humans. Both are endemic in Latin America, sub-Saharan Africa, India, vast parts of China, and South East Asia [115].

TLR4 and TLR2 play an important role in developing murine NCC caused by *Mesocestoides corti* [116]. The carbohydrate of *T. crassiceps* induces TLR4- and TLR2-mediated cytokine release (IL-6 and IL-4) [117]. However, molecules derived from *T. sodium* did not induce TLR2- or TLR4-mediated cytokine release in human lymphocytes [118]. Both *T. solium* and *T. crassiceps* express several glycolipids (GSL-1) and phospholipids that may act as PAMPs. *T. crassiceps* expresses lysophosphatidylcholine [119], also present on Schistosome, and triggers TLR2 response. Although the mechanism of these molecules inducing TLR signaling has not yet been evaluated, the host may use a similar pathway of this parasite recognition [120] (**Figure 6**).

5.4 Ascariasis

Phospholipids from schistosomes and *Ascaris* worm trigger TLR2, and lysophosphatidylserine can activate DCs to induce Th2 and IL-10-producing Treg [121].

5.5 Fasciolosis

F. hepatica tegumental antigens (FhTeg), *F. hepatica* ES, and ES-derived enzymes (thioredoxin peroxidase 2-Cys peroxiredoxin, fatty acid-binding protein) inhibit TLR4- and TLR3-mediated inflammatory response and facilitate parasite survival inside the host [122]. The protease activity of *F. hepatica* Cathepsin L1 (FheCL1) causes endosomal degradation of TLR3 and downregulates IL-1 production [123].

6. Conclusion

In conclusion, induction of TLR signaling pathway by infectious pathogen recognition provides a better understanding of innate immune defense mechanism against this disease. Immunotherapy emerges as a promising therapeutic approach for parasitic infection treatment over the past few years. Although no effective drugs have emerged, vaccine adjuvants yield promising results due to induction of cellular immunity via TLR. Large scales of clinical studies were conducted for developing potent and well-tolerated adjuvants. The protozoan and helminth parasites can cause activation (to a small degree) and negative regulation (to a larger degree) of TLRs resulting in increasing or decreasing parasite burden [103]. TLR agonists or antagonists are small molecule mimics, natural ligands used for treating Type I allergy, cancer, and infectious diseases. MF59 (Novartis) and AS04 (GSK) are some examples of TLR4 agonist licensed for human use [124]. GLA (TLR4 ligand) and

3M-052 (TLR7/8) ligands are now in clinical trial. Recently, RTS,S/AS01, a recombinant chimeric protein (c-terminal of circumsporozoite antigen fused with HPB antigen, and "ASO1" refers to the adjuvant formulation MPL and QS21, a natural glucoside), is used for treating Malaria [125]. Several new drugs have been chemically synthesized for better understanding of the interaction of TLRs with their ligands. The knowledge from these studies will provide a greater opportunity for developing plant-derived new therapeutic drugs. So, major efforts are required for targeting TLRs in pathological conditions.

Acknowledgements

CF is thankful to the Head of the Department of Zoology, Visva-Bharati University, for extending the facilities for her research work. AM is thankful to Science & Engineering Research Board (SERB), Department of Science & Technology, Govt. of India, for her JRF fellowship (grant no. ECR/2017/001028). DC is thankful to DBT for JRF. SD thanks UGC, New Delhi, for SRF. The authors are thankful to Dr. Rakesh Kundu and Dr. Sandip Mukherjee for their technical assistance and constant encouragement.

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

The authors thank the Head of the Department of Zoology, Visva-Bharati University, for providing the assistance in their research work.

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References

[1] Ropert C et al. Role of TLRs/MyD88 in host resistance and pathogenesis during protozoan infection: Lessons from malaria. Seminars in Immunopathology. 2008;**30**:41-51

[2] Chomel BB et al. Wildlife, exotic pets, and emerging zoonoses. Infectious Diseases. 2007;**13**:6-11

[3] Abbas AK, Lichtman AH. Cellular and Molecular Immunology; 2005;356-357

[4] Alicia K et al. Recognition of profilin by Toll-like receptor 12 is critical for host resistance to *Toxoplasma gondii*. Immunity. 2013;**38**:1-12

[5] Janeway CA Jr, Medzhitov R. Innate immune recognition. Annual Review of Immunology. 2002;**20**:197-216

[6] Akira S et al. Pathogen recognition and innate immunity. Cell. 2006;**124**:783-801

[7] Thompson MR et al. Pattern recognition receptors and the innate immune response to viral infection. Viruses. 2011;**3**(6):920-940

[8] Sivaprakasam R, et al. TLR specific immune responses against Helminth infections. Journal of Parasitology Research 2017: 9 p. Article ID: 6865789

[9] Mayank H, Veenu MH. Review. Toll-like receptors and their dual role in periodontitis: A review. Journal of Oral Science. 2011;**53**(3):263-271

[10] Medzhitov R et al. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. Nature. 1997;**388**:394-397

[11] Akira S, Takeda K. Toll-like receptor signalling. Nature Reviews. Immunology. 2004;**4**(7):499-511

[12] Dunne A, O'Neill LAJ. The interleukin-1 receptor/toll-like receptor superfamily: Signal transduction during inflammation and host defense. Science's STKE. 2003;**171**:3

[13] Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: Update on Toll-like receptors. Nature Immunology. 2010;**11**:373-384

[14] Yu L, Chen S. Toll-like receptors expressed in tumor cells: Targets for therapy. Cancer Immunology Immunotherapy. 2008;**57**:1271-1278

[15] Takeda K, Akira S. Toll-like receptors in innate immunity. International Immunology. 2005;**17**:1-1

[16] Pifer R et al. UNC93B1 is essential for TLR11 activation and IL-12-dependent host resistance to *Toxoplasma gondii*. The Journal of Biological Chemistry. 2011;**286**:3307-3314

[17] Blasius AL, Beutler B. Intracellular toll-like receptors. Immunity. 2010;**32**:305-315

[18] Doyle SL, O'Neill LA. Toll-like receptors: From the discovery of NF kappa B to new insights into transcriptional regulations in innate immunity. Biochemical Pharmacology. 2006;**72**:1102-1113

[19] Barton GM, Kagan JC. A cell biological view of Toll-like receptor function: Regulation through compartmentalization. Nature Reviews. Immunology. 2009;**9**:535-542

[20] Ulevitch RJ. Therapeutics targeting the innate immune system. Nature Reviews. Immunology. 2004;**4**:512-520

[21] Kanzler H et al. Therapeutic targeting of innate immunity with Toll-like receptor agonists and antagonists. Nature Medicine. 2007;**13**(5):552-559

[22] Ismaili J et al. Monophosphoryl lipid A activates both human dendritic cells and T cells. Journal of Immunology. 2002;**168**(2):926-932

[23] Barr TA et al. TLR-mediated stimulation of APC: Distinct cytokine responses of B cells and dendritic cells. European Journal of Immunology. 2007;**37**(11):3040-3053

[24] O'Neill LA. When signaling pathways collide: Positive and negative regulation of toll-like receptor signal transduction. Immunity. 2008;**29**:12-20

[25] Lye E et al. The role of interleukin 1 receptor-associated kinase 4 (IRAK-4) kinase activity in IRAK-4-mediated signaling. The Journal of Biological Chemistry. 2004;**270**:40653-40658

[26] Brown J et al. TLR-signaling networks: An integration of adaptor molecules, kinases, and cross-talk. Journal of Dental Research. 2011;**90**:417-427

[27] Botos I et al. The structural biology of Toll-like receptors. Structure. 2011;**19**:447-459

[28] Singh B et al. A large focus of naturally acquired *Plasmodium knowlesi* infections in human beings. Lancet. 2004;**363**:1017-1024

[29] Ockenhouse CF et al. Common and divergent immune response signaling pathways discovered in peripheral blood mononuclear cell gene expression patterns in presymptomatic and clinically apparent malaria. Infection and Immunity. 2006;**74**:5561-5573

[30] Scragg IG et al. Early cytokine induction by *Plasmodium falciparum* is not a classical endotoxin-like process. European Journal of Immunology. 1999;**29**:2636-2644

[31] Artavanis-Tsakonas K, Riley EM. Innate immune response to malaria: Rapid induction of IFN-gamma from human NK cells by live *Plasmodium falciparum*-infected erythrocytes. Journal of Immunology. 2002;**169**:2956-2963

[32] Walther M et al. Innate immune responses to human malaria: Heterogeneous cytokine responses to blood-stage *Plasmodium falciparum* correlate with parasitological and clinical outcomes. Journal of Immunology. 2006;**177**:5736-5745

[33] Clark IA, Rockett KA. The cytokine theory of human cerebral malaria. Parasitology Today. 1994;**10**:410-412

[34] Hisaeda H et al. Malaria: Immune evasion by parasites. The International Journal of Biochemistry & Cell Biology. 2005;**37**:700-706

[35] Gimenez F et al. Tumor necrosis factor alpha in the pathogenesis of cerebral malaria. Cellular and Molecular Life Sciences. 2003;**60**:1623-1635

[36] Thawani N et al. STAT6-mediated suppression of erythropoiesis in an experimental model of malarial anemia. Haematologica. 2009;**94**:195-204

[37] Krishnegowda G et al. Induction of proinflammatory responses in macrophages by the glycosylphosphatidylinositols of *Plasmodium falciparum*: Cell signaling receptors, glycosylphosphatidylinositol (GPI) structural requirement, and regulation of GPI activity. The Journal of Biological Chemistry. 2005;**280**:8606-8616

[38] Nebl T et al. Stimulation of innate immune responses by malarial glycosylphosphatidylinositol via pattern recognition receptors. Parasitology. 2005;**130**:S45-S62

[39] Durai P et al. Structure and dynamic behavior of Toll-like receptor 2 subfamily triggered by malarial

glycosylphosphatidylinositols of *Plasmodium falciparum*. The FEBS Journal. 2013;**280**:6196-6212

[40] Schofield L, Hackett F. Signal transduction in host cells by a glycosylphosphatidylinositol toxin of malaria parasites. The Journal of Experimental Medicine. 1993;**177**:145-153

[41] Zhu J et al. Induction of proinflammatory responses in macrophages by the glycosylphosphatidylinositols of *Plasmodium falciparum*: The requirement of extracellular signal-regulated kinase, p38, c-Jun N-terminal kinase and NF-kappaB pathways for the expression of proinflammatory cytokines and nitric oxide. The Journal of Biological Chemistry. 2005;**280**:8617-8627

[42] Schofield L et al. Glycosylphosphatidylinositol toxin of *Plasmodium* up-regulates intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin expression in vascular endothelial cells and increases leukocyte and parasite cytoadherence via tyrosine kinase-dependent signal transduction. Journal of Immunology. 1996;**156**:1886-1896

[43] Gazzinelli RT et al. Innate sensing of malaria parasites. Nature Reviews. Immunology. 2014;**14**:744-757

[44] Kalantari P et al. Dual engagement of the NLRP3 and AIM2 inflammasomes by plasmodium-derived hemozoin and DNA during malaria. Cell Reports. 2014;**6**:196-210

[45] Sharma S et al. Innate immune recognition of an AT-rich stem-loop DNA motif in the *Plasmodium falciparum* genome. Immunity. 2011;**35**:194-207

[46] Shio MT et al. Malarial hemozoin activates the NLRP3 inflammasome through Lyn and Syk kinases. PLoS Pathogens. 2009;**5**:e1000559

[47] Reimer T et al. Experimental cerebral malaria progresses independently of the Nlrp3 inflammasome. European Journal of Immunology. 2010;**40**:764-769

[48] Gbédandé K et al. Malaria modifies neonatal and early-life toll-like receptor cytokine responses. Infection and Immunity. 2013;**81**:2686-2696

[49] Baccarella A et al. Toll-like receptor 7 mediates early innate immune responses to malaria. Infection and Immunity. 2013;**81**:4431-4442

[50] Bargieri DY et al. New malaria vaccine candidates based on the *Plasmodium vivax* merozoite surface protein-1 and the TLR-5 agonist *Salmonella* Typhimurium FliC flagellin. Vaccine. 2008;**26**:6132-6142

[51] Bargieri DY et al. Immunogenic properties of are combinant fusion protein containing the C-terminal 19kDa of *Plasmodium falciparum* merozoite surface protein 1 and the innate immunity agonist FliC flagellin of *Salmonella* Typhimurium. Vaccine. 2010;**28**:2818-2826

[52] Fu Y et al. *Plasmodium yoelii* blood-stage primes macrophage-mediated innate immune response through modulation of toll-like receptor signalling. Malaria Journal. 2012;**11**:104

[53] Wu X et al. A malaria protein factor induces IL-4 production by dendritic cells via PI3K-AktNF-κB signaling independent of MyD88/TRIF and promotes Th2 response. The Journal of Biological Chemistry. 2018;**293**(27):10425-10434

[54] Travi B et al. Behavior of *Leishmania braziliensis* s.l. in golden hamsters: Evolution of the infection under different experimental

conditions. Journal of Parasitology. 1988;**74**(6):1059-1062

[55] Faria MS et al. Toll-like receptors in leishmania infections guardians or promoters? Journal of Parasitology Research. 2012;**2012**:930257

[56] Becker I et al. Leishmania lipophosphoglycan (LPG) activates NK cells through toll-like receptor-2. Molecular and Biochemical Parasitology. 2003;**130**:65-74

[57] Hawn TR et al. *Leishmania major* activates IL-1 alpha expression in macrophages through a MyD88-dependent pathway. Microbes and Infection. 2002;**4**:763-771

[58] Srivastava S et al. Leishmania expressed lipophosphoglycan interacts with Toll-like receptor (TLR)-2 to decrease TLR-9 expression and reduce anti-leishmanial responses. Clinical and Experimental Immunology. 2013;**172**:403-409

[59] Chandra D, Naik S. *Leishmania donovani* infection down-regulates TLR2-stimulated IL-12p40 and activates IL-10 in cells of macrophage/monocytic lineage by modulating MAPK pathways through a contact-dependent mechanism. Clinical and Experimental Immunology. 2008;**154**:224-234

[60] Silvestre R et al. The contribution of Toll-like receptor 2 to the innate recognition of a *Leishmania infantum* silent information regulator 2 protein. Immunology. 2009;**128**:484-499

[61] Saha S et al. *Leishmania donovani* exploits macrophage heme oxygenase-1 to neutralize oxidative burst and TLR signaling–dependent host defense. Journal of Immunology. 2019;**202**:1-14

[62] Srivastav S et al. *Leishmania donovani* exploits host deubiquitinating enzyme A20, a negative regulator of TLR signaling, to subvert host immune response. Journal of Immunology. 2012;**189**:924-934

[63] Filardy AA et al. Pro-inflammatory clearance of apoptotic neutrophils induces an IL-12 (low) IL-10 (high) regulatory phenotype in macrophages. Journal of Immunology. 2010;**185**:2044-2050

[64] de Veer MJ et al. MyD88 is essential for clearance of *Leishmania major*: Possible role for lipophosphoglycan and toll-like receptor 2 signaling. European Journal of Immunology. 2003;**33**:2822-2831

[65] Shweash M et al. *Leishmania mexicana* promastigotes inhibit macrophage IL-12 production via TLR-4 dependent COX-2, iNOS and arginase-1 expression. Molecular Immunology. 2011;**48**:1800-1808

[66] O'Neill LA. How Toll-like receptors signal: What we know and what we don't know. Current Opinion in Immunology. 2006;**18**:3-9

[67] Paun A et al. Critical role of IRF-5 in the development of T helper 1 responses to *Leishmania donovani* infection. PLoS Pathogens. 2011;**7**(1):e1001246

[68] Li Y et al. IL-18 gene therapy develops Th1-type immune responses in *Leishmania major*-infected BALB/c mice: Is the effect mediated by the CpG signaling TLR9? Gene Therapy. 2004;**11**:941-948

[69] Abou Fakher FH et al. TLR9-dependent activation of dendritic cells by DNA from *Leishmania major* favors Th1 cell development and the resolution of lesions. Journal of Immunology. 2009;**182**:1386-1396

[70] Ives A et al. Leishmania RNA virus controls the severity of mucocutaneous leishmaniasis. Science. 2011;**331**:775-778

[71] Zangger H et al. *Leishmania aethiopica* field isolates bearing an

endosymbiontic dsRNA virus induce pro-inflammatory cytokine response. PLoS Neglected Tropical Diseases. 2014;**8**(4):e2836

[72] Flandin JF et al. RNA interference reveals a role for TLR2 and TLR3 in the recognition of *Leishmania donovani* promastigotes by interferon-gamma-primed macrophages. European Journal of Immunology. 2006;**36**:411-420

[73] Bugue TA et al. Sleep structure: A new diagnostic tool for stage determination in sleeping sickness. Acta Tropica. 2005;**93**:107-117

[74] Jordan A. Tsetse flies as vectors of trypanosomes. Veterinary Parasitology. 1976;**2**:143-152

[75] Ramasawmy R et al. Heterozygosity for the S180L variant of MAL/TIRAP, a gene expressing an adaptor protein in the Toll-like receptor pathway, is associated with lower risk of developing chronic Chagas cardiomyopathy. The Journal of Infectious Diseases. 2009;**199**:1838-1845

[76] Almeida IC et al. Highly purified glycosylphosphatidylinositols from *Trypanosoma cruziare* potent proinflammatory agents. The EMBO Journal. 1999;**19**(7):1476-1485

[77] Oliveira AC et al. Expression of functional TLR4 confers proinflammatory responsiveness to *Trypanosoma cruzi* glycoinositolphospholipids and higher resistance to infection with *T. cruzi*. Journal of Immunology. 2004;**173**:5688-5696

[78] Ouaissi A et al. The *Trypanosoma cruzi* Tc52-released protein induces human dendritic cell maturation, signals via Toll-like receptor 2, and confers protection against lethal infection. Journal of Immunology. 2002;**168**:6366-6374

[79] Daniel NA et al. Distinct toll-like receptor signals regulate cerebral parasite load and interferona/band tumor necrosis factor–dependent T-cell infiltration in the brains of *Trypanosoma brucei*–infected mice. Journal of Infectious Diseases. 2012;**205**:320-332

[80] Bafica A et al. TLR9 and TLR2 signaling together account for MyD88-dependent control of parasitemia in *Trypanosoma cruzi* infection. Journal of Immunology. 2006;**177**:3515-3519

[81] Drennan MB et al. The induction of a type 1 immune response following a *Trypanosoma brucei* infection is MyD88 dependent. Journal of Immunology. 2005;**175**:2501-2509

[82] Pappas G et al. Toxoplasmosis snapshots: Global status of *Toxoplasma gondii* seroprevalence and implications for pregnancy and congenital toxoplasmosis. International Journal for Parasitology. 2009;**39**:1385-1394

[83] Luft BJ et al. Outbreak of central-nervous-system toxoplasmosis in western Europe and North America. Lancet (London England). 1983;**1**:781-784

[84] Jones JL et al. *Toxoplasma gondii* infection in the United States, 1999 2004, decline from the prior decade. The American Journal of Tropical Medicine and Hygiene. 2007;**77**:405-410

[85] Kousuke U et al. Transcriptional profiling of Toll-like receptor 2–deficient primary murine brain cell sduring *Toxoplasma gondii* infection. PLoS One. 2017;**12**(11):e0187703

[86] HA S-J et al. Internalization and TLR-dependent type I interferon production by inflammatory monocytes to *Toxoplasma gondii*. Immunology and Cell Biology. 2014;**92**(10):872-881

[87] Alan S et al. Innate recognition of *Toxoplasma gondii* in humans involves a mechanism distinct from that utilized

by rodents. Cellular & Molecular Immunology. 2017;**14**:36-42

[88] Barbalat R et al. Toll-like receptor 2 on inflammatory monocytes induces type I interferon in response to viral but not bacterial ligands. Nature Immunology. 2009;**10**:1200-1207

[89] Skariah S et al. *Toxoplasma gondii*: Determinants of tachyzoite to bradyzoite conversion. Parasitology Research. 2010;**107**:253-260

[90] Marie C, Petri WA Jr. Regulation of virulence of *Entamoeba histolytica*. Annual Review of Microbiology. 2014;**68**:493-520

[91] Maldonado-Bernal C et al. The innate immune response to *Entamoeba histolytica* lipopeptidophosphoglycan is mediated by toll-like receptors 2 and 4. Parasite Immunology. 2005;**27**(4):127-137

[92] Maldonado C, et al. Lipophosphopeptidoglycan of *Entamoeba histolytica* induces an antiinflammatory innate immune response and downregulation of toll-like receptor 2 (TLR-2) gene expression in human monocytes. Archives of Medical Research 2000;**31**(4, suppl. 4):S71-S73

[93] Kammanadiminti J et al. Regulation of Toll-like receptor-2 expression by the gallectin of *Entamoeba histolytica*. The FASEB Journal Expresse. 2003;**18**(1):155-157

[94] Catherine PA et al. Toll-like receptor 9-dependent macrophage activation by *Entamoeba histolytica* DNA. Infection and Immunity. 2008;**76**(1):289-297

[95] Brattig NW et al. The major surface protein of *Wolbachia endosymbionts* in filarial nematodes elicits immune responses through TLR2 and TLR4. Journal of Immunology. 2004;**173**(1):437-445

[96] Taylor MJ et al. Inflammatory responses induced by the filarial nematode *Brugia malayi* are mediated by lipopolysaccharide-like activity from endosymbiotic *Wolbachia* bacteria. The Journal of Experimental Medicine. 2000;**191**(8):1429-1436

[97] Martin I et al. *Fasciola hepatica* fatty acid binding protein inhibits TLR4 activation and suppresses the inflammatory cytokines induced by lipopolysaccharide in vitro and in vivo. Journal of Immunology. 2015;**194**(8):3924-3936

[98] Babu S, Nutman TB. Immunopathogenesis of lymphatic filarial disease. Seminars in Immunopathology. 2012;**34**: 847-861

[99] Venugopal PG et al. Activation and regulation of toll-like receptors (TLRs) by helminth parasites. Immunologic Research. 2009;**43**:252-263

[100] Kagan JC, Medzhitov R. Phosphoinositide-mediated adaptor recruitment controls Toll-like receptor signaling. Cell. 2006;**125**:943-955

[101] Goodridge HS et al. Immunomodulation via novel use of TLR4 by the filarial nematode phosphorylcholine-containing secreted product, ES-62. Journal of Immunology. 2005;**174**:284-293

[102] McManus DP, Loukas A. Current status of vaccines for schistosomiasis. Clinical Microbiology Reviews. 2008;**21**:225-242

[103] Sturrock RF. Schistosomiasis epidemiology and control: How did we get here and where should we go? Memórias do Instituto Oswaldo Cruz. 2001;**96**(Suppl):17-27

[104] Cha H et al. Differential pulmonic NK and NKT cell responses in *Schistosoma japonicum*-infected

mice. Parasitology Research. 2017;**116**(2):559-567

[105] Joshi AD et al. TLR3 modulates immunopathology during a *Schistosoma mansoni* egg-driven Th2 response in the lung. European Journal of Immunology. 2008;**38**(12):3436-3449

[106] La Flamme AC et al. Schistosomiasis decreases central nervous system inflammation and alters the progression of experimental autoimmune encephalomyelitis. Infection and Immunity. 2003;**71**(9):4996-5004

[107] Gao Y et al. Deficiency in TLR2 but not in TLR4 impairs dendritic cells derived IL-10 responses to schistosome antigens. Cellular Immunology. 2012;**272**(2):242-250

[108] Okano M et al. Induction of Th2 responses and IgE is largely due to carbohydrates functioning as adjuvants on *Schistosoma mansoni* egg antigens. Journal of Immunology. 1999;**163**(12):6712-6717

[109] Ritter M et al. *Schistosoma mansoni* triggers Dectin-2, which activates the Nlrp3 inflammasome and alters adaptive immune responses. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**(47):20459-20464

[110] Moreels TG et al. Concurrent infection with *Schistosoma mansoni* attenuates inflammation induced changes in colonic morphology, cytokine levels, and smooth muscle contractility of trinitrobenzene sulphonic acid-induced colitis in rats. Gut. 2004;**53**(1):99-107

[111] Velupillai P et al. B-1 cell (CD5+B220+) outgrowth in murine schistosomiasis is genetically restricted and is largely due to activation by polylactosamine sugars. Journal of Immunology. 1997;**158**(1):338-344

[112] Goodridge HS et al. Phosphorylcholine mimics the effects of ES-62 on macrophages and dendritic cells. Parasite Immunology. 2007;**29**(3):127-137

[113] Garcia HH, Del Brutto OH. Neurocysticercosis: Updated concepts about an old disease. Lancet Neurology. 2005;**4**(10):653-661

[114] Schantz PM. *Taenia solium* cysticercosis: An overview of global distribution and transmission. In: Singh G, Prabhakar S, editors. *Taenia solium* Cysticercosis from Basic to Clinical Science. Oxon, UK: CABI Publishing; 2002

[115] Garcia HH et al. Hyperendemic human and porcine *Taenia solium* infection in Peru. The American Journal of Tropical Medicine and Hygiene. 2003;**68**(3):268-275

[116] Mishra BB et al. MyD88-deficient mice exhibit decreased parasite-induced immune responses but reduced disease severity in a murine model of neurocysticercosis. Infection and Immunity. 2009;**77**(12):5369-5379

[117] Dissanayake S, Shahin A. Induction of interferon-gamma by *Taenia crassiceps* glycans and Lewis sugars in naive BALB/c spleen and peritoneal exudate cells. Molecular Immunology. 2007;**44**(7):1623-1630

[118] Uddin J et al. Mechanisms regulating monocyte CXCL8 secretion in neurocysticercosis and the effect of antiparasitic therapy. Journal of Immunology. 2010;**185**(7):4478-4484

[119] Baumeister S et al. Comparative serological reactivity of *Taenia crassiceps*, *Taenia solium* and *Taenia saginata* metacestode neutral glycolipids to infection serum from *Taenia crassiceps*-infected mice. Molecular and Biochemical Parasitology. 1992;**53**(1-2):53-61

[120] Mills GL et al. Lipid composition of metacestodes of *Taenia taeniaeformis* and lipid changes during growth. Molecular and Biochemical Parasitology. 1981;**3**(5):301-318

[121] Bradley JE, Jackson JA. Trichuriasis and ascariasis review article immunity, immunoregulation and the ecology of trichuriasis and ascariasis. Parasite Immunology. 2004;**26**:429-441

[122] Motran CC et al. Helminth infections: Recognition and modulation of the immune response by innate immune cells. Frontiers in Immunology. 2018;**9**:664(1-12)

[123] Donnelly S et al. Helminth cysteine proteases inhibit TRIF-dependent activation of macrophages via degradation of TLR3. The Journal of Biological Chemistry. 2010;**285**:3383-3392

[124] Fox CB et al. A nanoliposome delivery system to synergistically trigger TLR4 AND TLR7. Journal of Nanbiotechnology. 2014;**26**(12):17

[125] Kalantari P. The emerging role of pattern recognition receptors in the pathogenesis of malaria. Vaccine. 2018;**6**:13